PATENT COOPERATION TREA

PCT

C.D	UZF	בס צעעט	
WIPO		PCT	14-44

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

	licant's	•	ent's file reference	FOR FURTHER A	CTION	See Notificatio Preliminary Ex	n of Transmittal of International amination Report (Form PCT/IPEA/416)	
	International application No. International filing da PCT/EP 03/11239 10.10.2003			International filing date 10.10.2003	(day/mon	th/year)	Priority date (day/month/year) 18.10.2002	
	mation 8B37		ent Classification (IPC) or b	oth national classification	and IPC			
• • •	licant DIA FA	ARM	ACEUTICI S.P.A. et al					
1.	This Auti	s Inter hority	national preliminary examend is transmitted to the	mination report has bee applicant according to	en prepar Article 3	red by this Inte 6.	rnational Preliminary Examining	
2.	This	REP	ORT consists of a total of	of 7 sheets, including the	his cover	sheet.		
	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).							
	These annexes consist of a total of sheets.							
	•				 ,			
3.	This	repo	rt contains indications re	lating to the following it	ems:			
	1	\boxtimes	Basis of the opinion					
	11		Priority					
	Ш		Non-establishment of o	ppinion with regard to n	novelty, inventive step and industrial applicability			
	IV	\boxtimes	Lack of unity of invention			•	.,	
	٧	×	Reasoned statement u citations and explanation	nder Rule 66.2(a)(ii) wi	th regard atement	to novelty, inv	rentive step or industrial applicability;	
	VI		Certain documents cite				·	
	VII Certain defects in the international application							
٠.	VIII		Certain observations of	n the international appli	ication			
				•				
Date of submission of the demand Date of completion of this report								
17.05.2004					01.02.2	2005		
Name and mailing address of the international preliminary examining authority: Authorized Officer					Author Patienza.			
_		Eur	opean Patent Office		_		in the same	
161. 149 69 2099 - 0 1X. 523656 epiniu d				6 epmu d ·	Grassi,	D	((()	
-	<u> </u>	Fax: +49 89 2399 - 4465				ne No. +49 89 23	399-8499	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP 03/11239

 Basis of the repe 	ort
---------------------------------------	-----

1. With regard to the **elements** of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	De	scription, Pages					
	1-4	1	as originally filed				
	Cla	nims, Numbers	·				
	1-7	3	as originally filed				
•	Dra	awings, Figures	•				
	1-4		as originally filed				
	• •		as originally med				
With regard to the language, all the elements marked above were available or furnished to this Aulanguage in which the international application was filed, unless otherwise indicated under this item							
	The	These elements were available or furnished to this Authority in the following language: , which is:					
		the language of a tra	anslation furnished for the purposes of the international search (under Rule 23.1(b)).				
			lication of the international application (under Rule 48.3(b)).				
		the language of a tra Rule 55.2 and/or 55.	anslation furnished for the purposes of international preliminary examination (under .3).				
 With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing: 							
		contained in the inte	rnational application in written form.				
		filed together with th	e international application in computer readable form.				
		furnished subseque	ntly to this Authority in written form.				
		furnished subseque	ntly to this Authority in computer readable form.				
		The statement that t in the international a	he subsequently furnished written sequence listing does not go beyond the disclosure pplication as filed has been furnished.				
		The statement that t listing has been furn	he information recorded in computer readable form is identical to the written sequence ished.				
4.	The	amendments have r	esulted in the cancellation of:				
		the description,	pages:				
		the claims,	Nos.:				
		the drawings,	sheets:				

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP 03/11239

5.	This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).							
		(Any replacement sheet conta report.)	ining s	uch amendn	nents must be referred to under item 1 and annexed to this			
6.	Add	Additional observations, if necessary:						
IV.	. Lac	k of unity of invention	•					
1.	. In response to the invitation to restrict or pay additional fees, the applicant has:							
		restricted the claims.			·			
		paid additional fees.						
☐ paid additional fees under protest.								
	☑ neither restricted nor paid additional fees.							
2.	×	This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.						
3.	This	This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 s						
		complied with.						
	not complied with for the following reasons:							
	see	ee separate sheet						
4.	Con	Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:						
		all parts.			•			
	Ø	the parts relating to claims No	s. 1-26	,32-34,37-55	s(all part).			
٧.		Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement						
1	Statement :2.							
	Nov	elty (N)	Yes: No:	Claims Claims	1-26,32-34,37-55(all part)			
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-26,32-34,37-55(all part)			
	Indu	strial applicability (IA)	Yes: No:	Claims Claims	1-26,32-34,37-55(all part)			

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP 03/11239

see separate sheet

INTERNATIONAL PRELIMINARY

International application No. PCT/EP 03/11239

EXAMINATION REPORT - SEPARATE SHEET

Reference is made to the following documents:

D1: Lou et al., Bioconjugate Chem. 1999, 10, 755-762 (cited in the application).

D2: SPARER R. V. ET AL.: "Controlled Release from Glycosaminoglycan Drug Complexes" in "Controlled Release Delivery Systems" 1983, MARCEL DEKKER, NEW YORK, p. 107-119

Re Item IV

The International Examining Authority found multiple (groups of) inventions in this international application. No required additional examination fees were paid by the applicant. Consequently, this Written Opinion is restricted to the first invention (cf. below).

The closest state of the art for the present application is represented by D1. It discloses a HA-Taxol conjugate wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer comprising hydrazide groups.

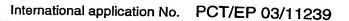
The technical problem underlying the present claims is seen in the provision of alternative conjugates of taxol conjugates with hyaluronic acid.

In view of the disclosure of D1 the alternative solutions claimed do not share a common special technical feature as required by Rule 13.2 PCT and the fact that the present proviso of claim 1 excludes the conjugate of D1 cannot establish unity among the different alternatives.

The following inventions appear to be present:

- a-1) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer, the bond between the spacer and the carboxyl groups of hyaluronic acid being an ester bond (cf. claims: 1-26, 32-34, 37-55, all part).
- a-2) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer, the bond between the spacer and the carboxyl groups of hyaluronic acid being amide bond (cf. claims 1 and 27).

.



- b) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid without spacer.
- c) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and OH groups of the hyaluronic acid.
- d) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and amino groups of deacetylated hyaluronic acid.

Re Item V

1) The subject-matter of present claims 1-26, 32-34, 37-55 (all part) is new (Article 33(2) PCT).

D1 discloses a HA-Taxol conjugate wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer comprising hydrazide groups. The present claims differ from D1 in that the bond between the spacer and the carboxyl groups of hyaluronic acid is an ester bond and not an (acid) hydrazide bond.

2) The subject-matter of claims 1-26, 32-34, 37-55 (all part) involves an inventive step (Article 33(3) PCT).

The closest state of the art for the present application is represented by D1 (cf. above).

The technical problem underlying the present claims is seen in the provision of alternative conjugates of taxol derivatives with hyaluronic acid.

In view of the test results (cf. page 35), the problem appears to be solved.

D2 discloses an other modified hyaluronic acid derivative in which the drug chloramphenicol is covalently attached to hyaluronic acid via amide linkage including an alanine bridge as an intermediate linking group (cf. page 111). The combination of D1 with D2 does not prompt the skilled person to the present conjugates involving a linker and an ester bond to HA. Consequently, inventive

INTERNATIONAL PRELIMINARY International application No. PCT/EP 03/11239 EXAMINATION REPORT - SEPARATE SHEET

14.

activity appears to be present.